Docket No.: 46906-2-DIV (71699)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Subroto CHATTERJEE

Examiner: M. Rao

Serial No.: 09/282,879

Group: 1652

Filed: March 31, 1999

For: RECOMBINANT N-SMASES AND NUCLEIC ACIDS ENCODING SAME

Mail Stop AF
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PO Box 1450
Alexandria, VA 22313-1450

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Patricia A. Barnes

Patricia A. Barnes

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Sir:

RESPONSE

In response to the Office Action dated October 25, 2004, Applicants request reconsideration of the application in view of the following amendments and remarks.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claims 1-12. Canceled.

13. (presently amended) A method for identifying a compound useful in the treatment of a human neutral sphingomyelinase related disorder, comprising

binding a human neutral sphingomyelinase cleavage target to a solid support,

contacting the solid support with a candidate pharmacological agent ~~with~~ and a recombinant human neutral sphingomyelinase having an amino acid sequence represented by SEQ ID NO. 2 or fragment thereof, ~~or a derivative of the amino acid sequence represented by SEQ ID NO. 2~~, the method further comprising ~~and~~ analyzing the mixture of the candidate agent, ~~and~~ human neutral sphingomyelinase or the fragment and the cleavage target ~~or the derivative~~,

wherein the analyzing step further comprises comparing enzyme activity in the presence and absence of the agent, wherein the fragment ~~or derivative~~ has at least about 50% of the activity of the protein of SEQ ID No. 2, and ~~wherein the fragment or derivative of the recombinant human neutral sphingomyelinase~~ is at least about 70% identical to the protein of SEQ ID No. 2

14. (original) The method of claim 13 wherein the human neutral sphingomyelinase has a sequence represented by SEQ ID NO:2.

15. (presently amended) The method of claim 13 wherein

1) a mixture is formed of i) the ~~I)a~~ human neutral sphingomyelinase cleavage target, ii) the human neutral sphingomyelinase or fragment ~~or derivative~~ thereof, and iii) a candidate pharmacological agent;

2) the mixture is treated under conditions whereby, but for the ~~present~~ presence of the candidate agent, the human neutral sphingomyelinase ~~of~~ or fragment ~~or~~

~~derivative~~ cleaves the cleavage target to yield ~~a~~ the cleavage product; and

3) the presence of the cleavage product is detected, wherein a reduced concentration of the cleavage product relative to a control mixture that does not contain the candidate agent identifies the candidate agent as a compound potentially useful in the diagnosis or treatment of a human neutral sphingomyelinase related disorder.

16. (original) The method of claim 15 wherein the human neutral sphingomyelinase cleavage target is sphingomyelin.

17.(previously presented) The method of claim 15 wherein the human neutral sphingomyelinase cleavage product is ceramide.

Claims 18-31. Canceled.

32. (presently amended) The method of claim 13, wherein the fragment ~~or derivative~~ of the recombinant human neutral sphingomyelinase is at least about 30 amino acids in length.

33. (presently amended) The method of claim 32, wherein the fragment ~~or derivative~~ of the recombinant human neutral sphingomyelinase is at least about 50 or 70 amino acids in length.

34. (presently amended) A method for identifying a compound useful in the treatment of a human neutral sphingomyelinase related disorder, comprising

contacting a candidate pharmacological agent with a recombinant human neutral sphingomyelinase having an amino acid sequence represented by SEQ ID NO. 2 and a human neutral sphingomyelinase cleavage target bound to a solid support, and analyzing the mixture of the candidate agent and human neutral sphingomyelinase,

wherein the analyzing step further comprises comparing enzyme activity in the presence and absence of the agent.

35. (presently amended) The method of claim 34 wherein,

1) a mixture is formed of i) ~~a~~ the human neutral sphingomyelinase cleavage target, ii) the human neutral sphingomyelinase, and iii) ~~a~~ the candidate pharmacological agent;

2) the mixture is treated under conditions whereby, but for the ~~present~~ presence of the candidate agent, the human neutral sphingomyelinase cleaves the cleavage target to yield ~~a~~ the cleavage product; and

3) the presence of the cleavage product is detected, wherein a reduced concentration of the cleavage product relative to a control mixture that does not contain the candidate agent identifies the candidate agent as a compound potentially useful in the treatment of a human neutral sphingomyelinase related disorder.

36. (previously presented) The method of claim 35 wherein the human neutral sphingomyelinase cleavage target is sphingomyelin.

37. (previously presented) The method of claim 36, wherein the human neutral sphingomyelinase cleavage product is ceramide.

REMARKS

Claims 13, 15, 32-35 have been amended. The claim amendments and new claims find support throughout the application including the Drawings and claims as filed originally.

Specific support for the amendment to claims 13 and 34 can be found at pg. 17, line 19 to pg. 18, line 7; pg. 19, lines 7-9 and Example 2 (disclosing, for instance, binding cleavage target to a solid substrate or support).

Other claim amendments have been made to improve claim clarity.

No new matter has been added by virtue of the claim amendment or new claims.

Applicants gratefully acknowledge withdrawal of prior rejections under §112, second paragraph, as indicated on pg. 2 of the Action.

Claim Objections

Each basis for objection to claims 15, 34 and 35 has been addressed. The Examiner's attention is gratefully acknowledged.

35 USC §112, second paragraph

Claims 13, 34, and 14, 16-17, 32-33 stand rejected as indefinite on grounds that it is not clear to the USPTO which agents are selected by the claimed method ie., those that reduce or increase enzyme activity. See pg. 3 of the Action, lines 7-9. Applicants respectfully disagree that the claims are indefinite in this respect at all.

As the specification makes clear, the claimed invention can be used to identify agents that increase or decrease activity of the human neutral sphingomyelinase (N-Smase) enzyme. See the specification at pg. 15, lines 25-29 and Example 2 (specifically pg. 32, lines 1-4), for instance.

See also pg. 3, lines 20-23. Typically, those agents that decrease activity will be especially useful. See pg. 3, line 22, for instance.

One reading the instant case would understand that the claimed invention method is flexible and can be used to identify agents that increase or decrease N-Smase activity. Further claim specificity is not required to make this concept clearer. Reconsideration and withdrawal of the rejection are requested.

35 USC §112, first paragraph (enablement)

Claims 13, 15-17, and 32-33 stand rejected as not being enabled for a method that involves use of derivatives of the N-Smase enzyme. While Applicants respectfully disagree with the position for reasons already of record, the issue has been addressed by this submission.

Applicants reason for deleting "derivative" is that the term is often used interchangeably with "fragment" in the specification. See pg. 8, lines 16-18, for instance. The amendments to claims 13, 14, 32, 33 in which "derivative" is removed is merely intended to clarify this point.

Applicants gratefully acknowledge that the Office has deemed the specification enabling for a method in which the recombinant N-Smase or fragment is used. See the Action at pg. 3.

In view thereof, reconsideration and withdrawal of the rejection are requested.

35 USC §112, first paragraph (written description)

Claims 13, 15-17 and 32-33 stand rejected as containing subject matter which was not described in the specification in such a way as to reasonably convey to one working in the field that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants cannot agree especially in view of the pending claims.

According to the *Guidelines for Examination of Patent Applications Under 35 USC §112, 1¶, "Written Description Requirement* (hereinafter "Guidelines"):

> The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, **as of the filing date sought,** applicant was in **possession** of the now claimed invention (citing *Vas-Cath, Inc.* 935 F.2d at 1563-64, 19USPQ2d at 1117).
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> See the Federal Register, Vol. 66, pp. 1099-1111, part IB at pg. 1105.

Thus, the appropriate inquiry is to confirm Applicants were in **possession** of the subject matter claimed **as of the application filing date**. The Guidelines are flexible and provide several ways in which possession of the claimed invention can be demonstrated as of Applicants' filing date:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in **possession of the claimed invention**, i.e., complete or partial structure, other **physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between structure and function, or some combination of such characteristics**. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.
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> Federal Register, *ibid*, part IIA at pg. 1106.

Indeed, the Federal Circuit has held that the written description requirement "may be satisfied by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention". See *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

In view of the specification, the pending claims fully satisfy the written description requirement set forth by the Guidelines and the Federal Circuit. Accordingly, there is no basis for the instant §112, first paragraph, written description rejection.

For instance, and as pointed out in the Appeal Brief and prior response, practice of the invention is not limited to any particular N-Smase so long as it can provide

acceptable function. See eg., pg. 15, lines 25-29 ; pg. 16, lines 4-15; and pg. 17, lines 8-10 of the present application (disclosing particular invention methods in which suitable enzyme fragments or derivatives are used). See also pg. 7, lines 19-26; Figures 1 and 2; pg. 8, lines 16-23; pg. 9, lines 1-20, for example.

Nucleic acids that encode such suitable N-Smases are provided at pg. 10, lines 12-24 of the present application. Nucleic acids having preferred base pair sizes and N-Smases having desired functional domains are provided at pg. 10, line 12 to pg. 11, line 4 of the present application. Suitable enzyme isoforms are taught at pg. 11, lines 21-25 of the present application.

In this regard, the USPTO has already determined that the specification satisfies the written description requirement under 35 USC §112 for the following nucleic acid claim taken from U.S. Patent No. 5,919,687 ("'687" predecessor of the instant case):

> Claim 9. An isolated nucleic acid that hybridizes to the sequence of SEQ ID NO:1 using a hybridization buffer comprising 20% formamide in 0.8M saline/0.08M sodium citrate (SSC) buffer at a temperature of 37.degree. C. and remaining bound to washing once with that SSC buffer at 37.degree. C., and that **codes for a functional human neutral sphingomyelinase or fragment which fragment has human neutral sphingomyelinase activity.**

See also claims 13-16 from the '687 patent (claiming various nucleic acid fragments that encode human neutral sphingomyelinase).

One of skill reading the instant application would readily appreciate that the application discloses isolated nucleic acids that can be used to make a variety of functional fragments of the human N-Smase enzyme. See claim 9 of the '687 patent, for instance. Methods for expressing the fragments from the isolated nucleic acids would be known to the worker reading Applicants' specification. See eg., pg. 11, line 26 to pg. 13, line 5; and Example 1, for example. See also Ausubel (of record and characterized by the Office as a "voluminous" cloning manual).

Moreover, the chemical structure of the native N-Smase has disclosed both at the amino acid and nucleic acid levels. See Figures 1 and 2, for example. Important function domains in the structure are recognized. See pgs. 10-11 of the application, for example. Methods for producing suitable N-Smases, preferably by use of conventional recombinant means have been disclosed. See pg. 11, line 27 to pg. 12, line 10 of the application.

Accordingly, it is believed that Applicants have fully satisfied the written description requirement. Reconsideration and withdrawal of the rejection are respectfully requested.

35 USC §103 (obviousness)

Claims 13-17 and 32-37 stand rejected as being unpatentable. See pgs. 11-15 of the Action. Applicants respectfully traverse for reasons already of record. Additional reasons follow.

Pending claim 13 recites a step in which the human neutral sphingomyelinase cleavage target is bound to a solid support. Claim 34 recites contact between the cleavage target, candidate agent, and enzyme.

In view thereof, the USPTO's combination of references is not the claimed invention. For instance, Chatterjee as cited does not teach the step of binding the cleavage target to the solid support or using bound cleavage target at all. Ogita and Ausbel as relied on do not remedy this defect as there is no teaching or suggestion in this regard.

A worker reading the specification would see the clear advantages of binding the neutral sphingomyelinase cleavage target to a solid support and using same according to the claimed method.

For instance, a wide variety of supports can be used and are compatible with binding to the cleavage target. See the specification at pg. 17, line 18 to pg. 19, line 10 and Example 2. Moreover, use of solid support to bind the cleavage target increases assay convenience (eg., support can be stored until needed, see Example 2). Further, and in embodiments in which the cleavage target is radiolabeled, the support can be readily transferred to a scintillation counter for analysis. For instance, see Example 2, lines 26-29.

None of these advantages are specifically taught or suggested by the USPTO's combination of Chatterjee, Ausbel and Ogita. Binding of the cleavage target is not taught or suggested. In particular, see pg. 12555, col. 2 under "Measurement of Sphingomyelinase Activity" in Chatterjee. See also pgs. 14-15 of the English translation of the Ogita reference.

Accordingly, reconsideration and withdrawal of the instant §103 rejection are respectfully requested.

CONCLUSION

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Although it is not believed that any further fee is needed to consider this submission, the Office is hereby authorized to charge our deposit account **04-1105** should such fee be deemed necessary.

Respectfully submitted,

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